

University of Groningen

Limiting factors of exercise performance 1 year after lung transplantation

Reinsma, G. D.; ten Hacken, N. H. T.; Grevink, R. G.; van der Bij, W.; Koer, G. H.; van Weert, E.

Published in:
Journal of Heart and Lung Transplantation

DOI:
[10.1016/j.healun.2006.08.008](https://doi.org/10.1016/j.healun.2006.08.008)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Reinsma, G. D., ten Hacken, N. H. T., Grevink, R. G., van der Bij, W., Koer, G. H., & van Weert, E. (2006). Limiting factors of exercise performance 1 year after lung transplantation. *Journal of Heart and Lung Transplantation*, 25(11), 1310-1316. <https://doi.org/10.1016/j.healun.2006.08.008>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Limiting Factors of Exercise Performance 1 Year After Lung Transplantation

G. D. Reinsma, MSc,^a N. H. T. ten Hacken, MD, PhD,^b R. G. Grevink, MD,^b W. van der Bij, MD, PhD,^b G. H. Koëter, MD, PhD,^b and E. van Weert, MSc^a

Background: After lung transplantation (LTx) exercise capacity frequently remains limited, despite significantly improved pulmonary function. The aim of this study was to evaluate maximal exercise capacity and peripheral muscle force before and 1 year after LTx, and to determine whether peripheral muscle force and lactate threshold (LT) limit exercise capacity 1 year after LTx.

Methods: Twenty-five subjects (mean age 43 years, 8 women and 17 men, 4 single-lung transplantations) were included in the study. Measurements included maximal exercise capacity, lactate threshold (symptom-limited bicycle ergometer test) and muscle force test (hand-held dynamometer) were performed before and 1 year after LTx.

Results: Before LTx, all patients showed severe exercise intolerance (mean \pm SD): work capacity (W_{peak}), 11.6 ± 18 W; peak oxygen uptake (VO_2), 8.6 ± 3.6 ml/min/kg. After LTx, exercise capacity improved significantly: W_{peak} , 69 ± 27 W ($p < 0.001$); peak VO_2 , 15.7 ± 4.3 ml/min/kg ($p < 0.001$). Ventilatory factors did not appear to limit exercise capacity. Quadriceps muscle force pre- vs post-LTx was: 248 ± 73 N vs 281 ± 68 N ($p < 0.05$). Post-LTx, a significant correlation was found between LT and exercise capacity ($r = 0.76$, $p < 0.001$), between muscle force and exercise capacity ($r = 0.41$, $p < 0.05$) and between the LT and muscle force ($r = 0.53$, $p < 0.01$).

Conclusions: The occurrence of an early and pathologic LT and peripheral muscle weakness contributes to the limitation of exercise capacity and reflects a peripheral deficit post-LTx. *J Heart Lung Transplant* 2006;25:1310–6. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Lung transplantation (LTx) has become an established mode of treatment for many forms of end-stage pulmonary disease. Upon recovery post-operatively, double-lung transplant (DLT) recipients typically have near-normal spirometry with mildly impaired diffusion capacity.¹ After single-lung transplantation (SLT), spirometry typically remains partially abnormal, reflecting the pathology of the remaining native lung.¹

Despite significantly improved pulmonary function, most transplant recipients have an exercise impairment as defined by lower-than-normal values of peak oxygen uptake (peak VO_2) and maximum achievable work rate (W_{peak}). VO_2 peak ranges from 40% to 60% of predicted

values, regardless of the transplantation type (single or double LTx) or underlying pulmonary disease.^{2–4} The reduced peak VO_2 is accompanied by low peak cardiac frequency, low oxygen pulse at peak exercise, high respiratory exchange ratio and early lactic acidosis, consistent with a defect originating in the peripheral muscles.³

Several studies have confirmed that muscle function changes after LTx. Pantoja et al demonstrated reduced peripheral muscle strength of the ankle dorsiflexor muscle groups between 11 and 102 months after LTx.⁵ Reduced total leg strength and work capacity were noted in another group of patients, most of whom were >18 months post-LTx.⁶ Reduced oxygen utilization by the vastus lateralis muscle was demonstrated after LTx by 31-phosphorus (^{31}P)-magnetic resonance spectroscopy and by optical near-infrared spectroscopy.^{7,8} Skeletal muscle biopsies from the quadriceps exhibited lower activity of the oxidative enzymes, lower proportion of type 1 (fatigue-resistant) fibers, higher lactate concentration, low intramyocyte pH, and reduced adenosine triphosphate (ATP) content.⁹ Together, these studies support the hypothesis that the limited exercise capacity found after LTx may be due, at least in part, to limited muscle strength and limited endurance capacity of the lower limbs.

From the ^aCenter for Rehabilitation and ^bDepartment of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Submitted March 17, 2006; revised July 6, 2006; accepted August 20, 2006.

Reprint requests: G. D. Reinsma, MSc, Center for Rehabilitation, University Medical Center Groningen, University of Groningen, Hanzeplein 1, P.O. Box 30001, 9700 RB Groningen, The Netherlands. Telephone: +31-50-3613651. Fax: +31-50-3611708. E-mail: g.d.reinsma@rev.umcg.nl

Copyright © 2006 by the International Society for Heart and Lung Transplantation. 1053-2498/06/\$-see front matter. doi:10.1016/j.healun.2006.08.008

Table 1. Baseline Characteristics of Participating Subjects

Disease	Transplant type (SLT/DLT)	Gender (M/F)	Age (years)	BMI (kg/m ²)	FEV ₁ /FVC (%)	TLC (% predicted)	Quadriceps force (% predicted)	Peak load (W)
Emphysema	SLT	F	41	17.4	27.0	128.0	85.7	0
Emphysema	SLT	F	50	21.1	21.0	111.8	50.2	0
Emphysema	DLT	F	37	18.3	21.5	130.6	58.7	10
Emphysema	DLT	F	45	22.9	28.6	94.3	69.6	30
Emphysema	DLT	F	45	23.3	29.1	120.3	120.9	0
Emphysema	DLT	F	50	22.7	27.3	83.2	49.4	0
Emphysema	DLT	F	51	28.3	27.3	104.0	54.8	10
Emphysema	DLT	F	54	24.3	26.7	111.5	68.5	0
Emphysema	DLT	F	56	20.1	55.8	61.0	39.2	0
Emphysema	DLT	M	44	15.9	17.7	ND	72.6	0
Emphysema	DLT	M	52	21.1	30.0	117.0	63.0	0
Cystic fibrosis	DLT	F	29	17.9	59.2	62.8	62.7	40
Cystic fibrosis	DLT	F	38	21.3	44.8	60.9	35.0	0
Cystic fibrosis	DLT	F	38	21.0	55.8	52.2	59.4	30
Cystic fibrosis	DLT	M	17	15.2	52.0	69.7	35.7	30
Cystic fibrosis	DLT	M	35	18.2	34.1	104.0	57.7	0
Pulmonary fibrosis	SLT	F	39	24.2	81.5	26.6	86.3	0
Pulmonary fibrosis	SLT	M	42	25.4	60.8	48.0	58.4	60
Pulmonary fibrosis	DLT	M	41	27.1	81.0	43.8	40.6	50
Pulmonary fibrosis	DLT	M	53	28.7	82.0	47.0	69.4	20
Pulmonary fibrosis	DLT	M	55	23.1	73.5	63.4	69.8	0
Bronchiectasis	DLT	F	48	23.3	32.0	74.2	57.3	0
Bronchiectasis	DLT	F	56	21.2	82.6	38.0	80.1	0
LAM	DLT	F	34	18.6	25.5	116.0	57.2	0
Eisenmenger syndrome	DLT	F	21	18.7	85.1	60.0	62.7	10
Mean	4 SLT	8 F	43	21.6	46.5	80.3	62.0	11.6
SD	21 DLT	17 M	(10)	(3.6)	(23.4)	(31.7)	(18.6)	(18.0)

SLT, single-lung transplant; DLT, double-lung transplant; BMI, body mass index; FEV₁/FVC, forced volume in 1 second as percentage of forced vital capacity; TLC, total lung capacity; LAM, lymphangio-leiomyomatosis; ND, not determined; 0 W, not completing 3 minutes of unloaded cycling.

The question arises as to when exactly peripheral muscle performance deteriorates. After LTx, factors such as immobilization, poor nutritional status, catabolic conditions and pharmacologic treatment with corticosteroids or calcineurin inhibitors may contribute to peripheral muscle wasting or dysfunction. However, already before LTx the underlying pulmonary disease may result in peripheral muscle deconditioning and atrophy. Indeed, in the pre-transplant condition of chronic obstructive pulmonary disease (COPD) a marked reduction in type 1 fiber proportion, reduced muscle mass, and decreased concentrations of oxidative enzymes in the quadriceps femoris have been reported.¹⁰

Until now, there has been, to our knowledge, little information available regarding exercise performance and peripheral muscle function before and after lung transplantation, at well-defined time-points. Therefore, the primary aim of the present study was to evaluate in a longitudinal manner the limitations of maximal exercise capacity together with peripheral muscle force before and 1 year after LTx. We hypothesized that peripheral muscle weakness is an important contribut-

ing factor in the limitation of exercise at 1 year post-transplantation.

METHODS

Patients

The patients studied were a cohort of single- and double-lung transplantation (SLT and DLT, respectively) recipients at the University Medical Center Groningen (UMCG, The Netherlands). Twenty-five patients (4 SLTs, 21 DLTs) who survived >1 year after transplantation were studied both before (mean \pm SD: 620 \pm 477 days) and 1 year after transplantation. All patients had end-stage respiratory disease: emphysema ($n = 11$); idiopathic pulmonary fibrosis ($n = 5$); cystic fibrosis ($n = 5$); bronchiectasis ($n = 2$); Eisenmenger's syndrome ($n = 1$); and lymphangio-leiomyomatosis ($n = 1$). None of the recipients had undergone re-transplantations. Baseline patient characteristics are shown in Table 1. After discharge, all patients were instructed to exercise (walking, cycling, etc.) regularly, without a prescribed structured exercise program, supervised by a physiotherapist. All transplant recipients received conventional immunosuppression with cyclosporine (CyA) or

tacrolimus (FK) (48% CyA and 52% FK), azathioprine or mycophenolate (87.5% and 12.5%) and prednisone (100%). Hemoglobin concentration was measured in all transplant recipients (mean \pm SD: men, 7.45 ± 0.96 mmol/liter; women, 6.69 ± 0.74 mmol/liter). Approval for the use of clinical data in this study was obtained from our institutional review board on human research. Written informed consent was obtained from all patients.

Pulmonary Function

Flow volume measurements included forced expiration volume in 1 second (FEV₁) and inspiratory vital capacity (IVC). Total lung capacity (TLC) and functional residual capacity (FRC) were measured by body plethysmography (Jaeger, Wurzburg, Germany). Values were expressed as a percentage of reference values.¹¹ All measurements were performed according to European Respiratory Society (ERS) standards.¹²

Peripheral Muscle Force

Maximal voluntary isometric muscle force of the musculi quadriceps, biceps brachii and triceps brachii were measured bilaterally using a hand-held dynamometer (MicroFET II, Hoggan Health Industries, Draper, UT). All actions were tested in gravity-neutralized positions, with the exception of knee extension. During the quadriceps force measurement, the patients were sitting on a table and the dynamometer was positioned at the ventral side of the leg just proximal to the ankle. The force of the biceps brachii and triceps brachii was measured while the patient was in a supine position. The upper arm rested horizontally with the elbow in 90° flexion. For the biceps brachii measurement the dynamometer was placed on the ventral side of the arm just proximal to the wrist joint. The triceps brachii was measured with the dynamometer placed on the dorsal side of the arm just proximal to the wrist joint. During all measurements the break method was used. In utilizing this method, the examiner gradually overcomes the force produced by the patient until the extremity gives away.¹³ All measurements were performed three times. Mean muscle force values of the dominant side were calculated and used for analyses. Predicted values were calculated using the equations of Bohannon.¹⁴

Cardiopulmonary Exercise Testing

Maximal exercise capacity was measured using an incremental symptom-limited bicycle ergometer test. Heart rate and rhythm were monitored by electrocardiography. A brachial or radial artery catheter was inserted for periodic sampling of blood for analysis of pH, Pao₂, Paco₂ and lactate. Samples were drawn at rest and every 3 minutes during exercise, in the last 45 seconds of each increment. Patients respired through a mouth-

piece and wore a nose-clip. Minute ventilation (V_E), oxygen uptake (Vo₂) and carbon dioxide output (Vco₂) were measured and calculated from a mixing chamber every 30 seconds (MMC Oxygen Champion, Jaeger, Wurzburg). Calibration of gas analyzers and flow transducers was performed before each test. The test required 3 minutes of seated rest on the ergometer for collecting baseline measurements. Subjects were then instructed to begin pedaling at 60 to 70 revolutions per minute. After 3 minutes of unloaded cycling, power was increased every 3 minutes by 15 W. The patients were encouraged to cycle as long as possible. Peak values for all variables were obtained by averaging data over the last 20 seconds of maximum completed work. Peak Vo₂ was predicted using formulas for healthy subjects.¹⁵ Peak V_E was predicted by the formula of Carter ($37.5 * FEV_1$).¹⁶ The lactate threshold (LT) was determined by plotting the log lactate concentration against the log Vo₂ and taking the break-point of the slope. The LT was expressed as percentage of predicted peak Vo₂.¹⁷

To determine the limiting factor during exercise the following definitions were used: cardiocirculatory limitation was defined as having no heart rate reserve (peak heart rate at or above predicted peak heart rate); ventilatory limitation was defined as having a breathing reserve of <11 liters/min and/or a Pco₂ becoming >6 kPa¹⁵; oxygen uptake limitation was defined as an increase in alveolar-arterial oxygen tension of >2 kPa during exercise¹⁸; and peripheral muscle limitation was defined as having none of the other limitations in combination with a low lactate threshold (<40% of predicted Vo₂).¹⁵

Statistics

Statistical analysis was performed using SPSS/PC+11 software. Shapiro-Wilk tests were used to determine whether variables of interest were normally distributed. Differences pre- and post-LTx were analyzed using the Student's *t*-test for paired samples (for normally distributed variables) and Wilcoxon tests (in case of skewed distribution). *p* < 0.05 was considered statistically significant. Correlations between variables were investigated using the 2-tailed Pearson's correlation coefficient (for normally distributed variables) and Spearman's correlation coefficient (in case of skewed distribution).

RESULTS

Pulmonary Function Before and 1 Year After LTx

After LTx dynamic lung volumes (FEV₁, FVC) improved significantly in all transplant recipients, in contrast to static lung volumes (TLC) (Table 2). Also, Pao₂ and Paco₂ at rest improved significantly (Table 2).

Table 2. Pulmonary Function Before and 1 Year After LTx

	Baseline (n = 25)	At 1 year after LTx (n = 25)	p-value
FEV ₁ (liters)	0.94 (0.52)	2.65 (0.96)	<0.001
% predicted	28.5 (12.8)	83.4 (27.3)	<0.001
FVC (liters)	2.15 (0.69)	3.30 (0.89)	<0.001
% predicted	52.2 (16.9)	85.6 (22.6)	<0.001
FEV ₁ /FVC (%)	46.5 (23.4)	79.9 (16.1)	<0.001
TLC (liters)	4.55 (1.88)	4.67 (1.01)	0.71
% predicted	80.3 (31.7)	81.7 (16.2)	0.81
Pao ₂ at rest (kPa)	8.2 (1.3)	12.1 (1.2)	<0.001
Paco ₂ at rest (kPa)	5.7 (1.3)	5.0 (0.5)	0.004

Values expressed as mean (SD); FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; Pao₂, arterial oxygen tension; Paco₂, arterial carbon dioxide tension.

Exercise Capacity Before and 1 Year After LTx

Before LTx, peak VO₂ and W_{peak} were below normal values in all recipients (Table 3). The limitations in exercise, as defined in the Methods section, were caused by impaired ventilation in 21 patients and by impaired oxygen uptake in 4 patients. Before LTx, the lactate threshold could not be determined in 15 patients because of peak workloads of 0 W. In the remaining 10 subjects, lactate threshold was 22.4 ± 9.7% (mean ± SD) of the predicted peak VO₂.

After LTx, all recipients showed significant improvements in peak VO₂ and W_{peak} (Table 3). Peak VE and VO₂ improved approximately 2-fold, and peak workload 6-fold. Nevertheless, mean VO₂max and W_{peak} remained significantly below normal values. Limited exercise capacity was not due to high heart rate, impaired ventilation or low oxygen uptake. The average lactate threshold was 30.0 ± 11.3% of predicted peak VO₂. Thus, in all subjects the criteria for peripheral muscle limitation were met. However, 8 patients also showed an increase in alveolar-arterial oxygen tension of >2 kPa at maximal exercise, indicating an oxygen uptake limitation in combination with a peripheral limitation. There were no significant differences between patients treated with CyA and patients treated with FK (peak oxygen uptake in the CyA group was 15.5 ml/min/kg vs 15.9 ml/min/kg in the FK group; lactate threshold was 31% in the CyA group vs 29% in the FK group; Table 4). No significant correlations (Spearman) were found between doses of corticosteroid and peak VO₂ ($r = 0.30$, $p = 0.15$) and between doses of corticosteroid and lactate threshold ($r = 0.12$, $p = 0.58$). A weak, but significant correlation (Spearman) was found between time on the waiting list and muscle force of the quadriceps ($r = -0.44$, $p = 0.03$). This correlation suggests that lung transplant recipients with a long waiting time have less muscle force of the quadriceps 1 year after transplantation.

Peripheral Muscle Force and Its Contribution to Limitation of Exercise 1 Year After LTx

Upper-extremity muscle force improved significantly (biceps: 168 ± 53 N to 192 ± 58 N, $p = 0.01$; triceps: 117 ± 36 N to 130 ± 33 N, $p = 0.02$). One year after LTx, muscle force of the biceps was 101 ± 17% of predicted values and muscle force of the triceps was 95 ± 28% of predicted values. Muscle force of the lower limbs (quadriceps) improved significantly from 248 ± 73 N to 281 ± 68 N and reached a value of 67 ± 19 N of predicted (Table 5). The predicted values of muscle force (corrected for weight) did not show significant improvement.

After LTx, muscle force of the quadriceps correlated significantly with the peak load ($r = 0.41$, $p < 0.05$). There was also a significant correlation between the lactate threshold and peak load ($r = 0.76$, $p < 0.001$) and peak VO₂ ($r = 0.68$, $p < 0.001$). After LTx, quadriceps muscle force correlated significantly with lactate threshold ($r = 0.53$, $p < 0.01$) (Figure 1). The correlation between biceps muscle force and the LT just failed to reach significance ($r = 0.37$, $p < 0.07$) and

Table 3. Maximal Exercise Capacity and the Limiting Factors

	Baseline	At 1 year after LTx
Peak load (W)	11.6 (18.0)	68.6 (27.3) ^b
% predicted	7.4 (10.8)	50.8 (17.5) ^b
Cardiac		
Peak heart rate	117 (19)	135 (17) ^b
Heart rate reserve (beats/min)	60 (19)	40 (18) ^b
Ventilatory		
Peak VE exercise (liters/min)	21.0 (10.6)	42.4 (14.1) ^b
% predicted	62.7 (19.3)	46.1 (17.8) ^a
Breathing reserve (liters/min)	14.3 (12.7)	56.8 (31.8) ^b
Vd/Vt at max (%)	51.8 (8.7)	26.8 (8.5) ^b
Paco ₂ at max (kPa)	5.8 (1.3)	4.8 (0.9) ^b
Oxygen uptake		
Peak VO ₂ (ml/min/kg)	8.6 (3.6)	15.7 (4.3) ^b
% predicted	28.3 (9.4)	56.8 (14.8) ^b
Pao ₂ at max (kPa)	7.4 (1.1)	11.7 (2.1) ^b
Increase in Aao ₂ (kPa)	1.02 (1.41) ^c	1.70 (1.27) ^{a,c}
Sao ₂ at max (%)	88 (5)	96 (2) ^b
Peripheral muscle		
Lactate at max (mmol/liter)	2.5 (2.2)	7.3 (2.6) ^b
LT (ml/min VO ₂)	477 (251) ^d	541 (174) ^d
	—	576 (241) ^e
LT (% predicted VO ₂)	22.4 (9.7) ^d	28.1 (11.3) ^d
	—	30.0 (11.3) ^e

Values expressed as mean (SD); Paco₂, arterial carbon dioxide tension; Aao₂, alveolar-arterial oxygen tension difference; Vd/Vt, dead-space ventilation; LT, lactate threshold.

^a $p < 0.05$ vs baseline.

^b $p < 0.01$ vs baseline.

^cValues of 24 subjects.

^dValues of 10 subjects.

^eValues of 25 subjects.

Table 4. Differences in Exercise Performance and Lactate Threshold (LT) Between Patients Treated With Cyclosporine (CyA) and Patients Treated With Tacrolimus (FK)

	CyA (N = 12)	FK (N = 13)	Mean difference	p-value
Peak VO_2 (ml/min/kg)	15.5 (3.6)	15.9 (5.0)	-0.39	0.825
LT (% predicted VO_2)	31.3 (10.0)	28.9 (12.6)	2.47	0.594

Values expressed as mean (SD); peak VO_2 , peak oxygen uptake; LT, lactate threshold.

triceps muscle force did not significantly correlate with LT ($r = 0.30$, $p < 0.15$).

DISCUSSION

This study has demonstrated that maximal exercise capacity (W_{peak} and VO_2max) improved significantly 1 year after LTx. However, maximal exercise capacity did not reach normal values, despite (near) normal lung function in most recipients. After LTx, maximal exercise capacity was reduced due to peripheral muscle limitation in all recipients, which was reflected by pathologically low lactate thresholds. Peak muscle force of the quadriceps improved modestly after LTx, but remained low compared with age-, gender- and weight-adjusted reference values. This is the first study demonstrating, at well defined time-points, that peripheral peak muscle force plays an important role in the limited exercise capacity after LTx, in line with the hypothesis.

This study demonstrated clearly that exercise capacity is significantly limited 1 year after LTx, which is completely in line with previous findings.^{2-4,19,20} Despite the fact that the LTx recipients were studied in a stable clinical condition, they achieved peak VO_2 at approximately 57% of predicted.

In contrast to pre-transplant exercise results there was no evidence of a ventilatory limitation during maximal exercise testing 1 year after LTx. Most patients did not reach the predicted maximal heart frequency. In DLT recipients, cardiac denervation may have been responsible for the lower peak heart rate. However, all DLT recipients underwent operation using bilateral (sequential single) LTx, which makes primary disturbance in cardiac function rather unlikely. All transplant recipients showed signs of lactic acidosis at an abnor-

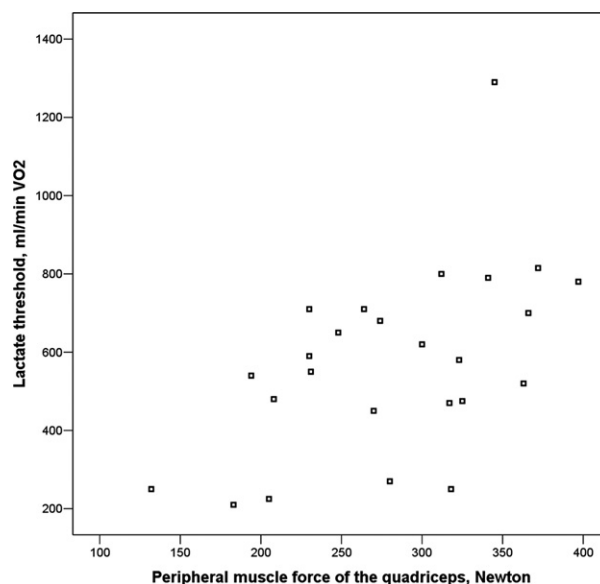
mally low workload. All 25 LTx recipients had a pathologic lactate threshold of $<40\%$ of the predicted value. Schwaiblmair and colleagues³ also demonstrated a reduced LT within 3 months after transplantation. Accordingly, Gibbons et al²¹ investigated 12 SLT recipients within 7 months after transplantation and observed a low LT. In the absence of a ventilatory, oxygen uptake or cardiac limitation, these data indicate that peripheral muscle dysfunction is a major cause of decreased exercise capacity after LTx. However, 8 patients also showed an increase in alveolar-arterial oxygen tension of >2 kPa at maximal exercise, indicating a peripheral limitation in combination with an oxygen uptake limitation.

One component of peripheral muscle dysfunction is the decreased aerobic capacity, as reflected by a low LT. Decreased aerobic capacity may be due to muscle depletion (especially loss of slow-twitch fibers), and to impaired aerobic enzyme deficits. Interestingly, cyclosporine has been shown to inhibit skeletal muscle mitochondrial respiration in vitro and to diminish endurance exercise time in rats. The mechanisms involved are not clear, but seem to be related to diminished mitochondrial calcium efflux with subsequent mito-

Table 5. Muscle Force Before and 1 Year After LTx

	Baseline (n = 25)	At 1 year after LTx (n = 25)	p-value
Quadriceps muscles (N)	248 (73)	281 (68)	0.02
% predicted	62.0 (18.6)	66.7 (18.6)	0.23
Triceps muscles (N)	117 (36)	130 (33)	0.02
% predicted	90.0 (28.1)	95.8 (21.2)	0.17
Biceps muscles (N)	168 (53)	192 (58)	0.01
% predicted	94.3 (28.0)	101.1 (17.0)	0.15

Values expressed as mean (SD); N, newtons.

**Figure 1.** Scatterplot of the lactate threshold vs peripheral muscle force of quadriceps ($r = 0.53$, $p < 0.01$) 1 year after lung transplantation.

chondrial dysfunction.^{22,23} One year after transplantation there were no differences in aerobic capacity between patients treated with CyA and those treated with FK. Cyclosporine may also cause chronic anemia in transplant recipients, resulting in reduced oxygen-carrying capacity of the blood. However, all transplant recipients have maintained normal or mildly reduced hemoglobin values. Additional effects of medication, such as doses of corticosteroid, were also not related to aerobic capacity and lactate threshold.

Another component of peripheral muscle dysfunction is decreased peak muscle force. Our data show that the mean peak muscle force of the quadriceps was decreased in LTx recipients compared with reference values. This may have been due to immobilization, sub-optimal nutrition, catabolic conditions, critical illness neuropathy and pharmacologic treatment.²⁴ Indeed, potentially toxic medications are administered to all transplant recipients. For example, systemic steroids, frequently prescribed pre- and post-LTx, may induce atrophy and myopathy in all peripheral muscles.⁷ Our data also show a significant, but weak correlation between time on the waiting list and muscle force of the quadriceps 1 year after transplantation. This correlation suggests that lung transplant recipients with a long waiting period have less muscle force 1 year after transplantation. However, time on the waiting list does not provide information about disease duration before assessment. Based on these data we could not determine the influence of disease duration on muscle force.

The results of this study suggest that both the muscle aerobic capacity and muscle peak force may contribute to the limited exercise capacity observed after LTx. However, the direction of a possible causal relationship between muscle force and exercise capacity is unclear, as limited exercise capacity may lead to decreased physical activities and muscle deconditioning and vice versa. An explanation for the positive correlation between peak quadriceps muscle force and the anaerobic threshold may be that patients with less muscle volume develop greater muscle tone at sub-maximal workloads, resulting in impaired peripheral blood flow and early lactate production. To help determine the role of pre-transplant deconditioning vs possible effects of immunosuppressive medications, further comparable studies of, for example, other organ transplant groups, would be informative.

Previous studies detected LT by gas exchange,¹⁵ which is an indirect and non-invasive method. In contrast, in the present study LT was assessed by measuring the lactate concentration directly, and by plotting the log blood lactate against the log $\dot{V}O_2$ and taking the break-point of the slope.¹⁷ This method detects the LT more reliably, because atypical records due to irregular breathing or a poor ventilatory response to metabolic

acidosis can be obviated. Despite this advantage, it was not possible to detect LT in 15 subjects pre-LTx. Due to early termination of the test, it was not possible to reach LT.

To our knowledge, only a few studies^{25,26} have examined the effects of a rehabilitation program on recipients of lung transplants. One study²⁵ of 11 heart-lung transplant recipients used an in-hospital exercise training program lasting 20 to 70 days and consisting of supervised incremental treadmill walking, inspiratory muscle training, abdominal muscle training and upper- and lower-extremity weight training. Skeletal (flexor and extensor leg muscles) and respiratory muscle function and exercise capacity improved with time, but were still below normal values after 18 months. In another study,²⁶ a 6-week aerobic exercise training program improved peak work and oxygen consumption in lung transplant recipients; however, these improved values were still only 55% to 65% of those of control subjects, and all transplant recipients stopped exercising due to leg pain. No change was observed in lactate production and LT, which may indicate that improvements in skeletal muscle oxidative capacity did not occur.

Our study may have practical implications for pre- and post-LTx rehabilitation, although our results must be interpreted with care due to the small number of patients. Unfortunately, we did not have accurate data on the exact exercise programs followed by the lung transplant recipients. However, the association between muscle force and lactate threshold in the present study may underline the importance of early progressive resistance training or high-intensity interval anaerobic training. The usefulness of resistance training, as a supplement to conventional aerobic exercise, has been clearly shown in patients with COPD and CF.²⁷⁻³⁰ It is difficult to determine whether the training stimulus used in previous studies was adequate for providing an improvement in exercise capacity and LT. Therefore, the optimal training strategies for lung transplant recipients remain to be determined in further research.

A potential limitation of this study is the heterogeneous study population, consisting of six different diseases. On the other hand, there is a universal problem of limited exercise capacity after LTx due to muscle performance. Apparently, the post-LTx factors responsible for this muscular deficit are present, irrespective of the underlying disease.

In conclusion, exercise capacity is reduced in lung transplant recipients. Despite (near) normal lung function, all patients demonstrated an early and pathologic lactate threshold, even 1 year after transplantation. The presence of early, pathologic lactate threshold and peripheral muscle weakness contributes to the limita-

tion of exercise capacity and reflects a peripheral deficit post-LTx.

REFERENCES

- Williams TJ, Snell GI. Early and long-term functional outcomes in unilateral, bilateral, and living-related transplant recipients. *Clin Chest Med* 1997;18:245-57.
- Levy RD, Ernst P, Levine SM, et al. Exercise performance after lung transplantation. *J Heart Lung Transplant* 1993;12:27-33.
- Schwaiblmair M, Reichenspurner H, Muller C, et al. Cardiopulmonary exercise testing before and after lung and heart-lung transplantation. *Am J Respir Crit Care Med* 1999;159:1277-83.
- Williams TJ, Patterson GA, McClean PA, Zamel N, Maurer JR. Maximal exercise testing in single and double lung transplant recipients. *Am Rev Respir Dis* 1992;145:101-5.
- Pantoja JG, Andrade FH, Stoki DS, Frost AE, Eschenbacher WL, Reid MB. Respiratory and limb muscle function in lung allograft recipients. *Am J Respir Crit Care Med* 1999;160:1205-11.
- Lands LC, Smountas AA, Mesiano G, et al. Maximal exercise capacity and peripheral skeletal muscle function following lung transplantation. *J Heart Lung Transplant* 1999;18:113-20.
- Evans AB, Al Himyary AJ, Hrovat MI, Pappagianopoulos P, et al. Abnormal skeletal muscle oxidative capacity after lung transplantation by ³¹P-MRS. *Am J Respir Crit Care Med* 1997;155:615-21.
- Tirdel GB, Girgis R, Fishman RS, Theodore J. Metabolic myopathy as a cause of the exercise limitation in lung transplant recipients. *J Heart Lung Transplant* 1998;17:1231-7.
- Wang XN, Williams TJ, McKenna MJ, et al. Skeletal muscle oxidative capacity, fiber type, and metabolites after lung transplantation. *Am J Respir Crit Care Med* 1999;160:57-63.
- Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999;159(suppl):S1-40.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report of Working Party Standardization of Lung Function Tests, European Community for Steel and Coal Official Statement of the European Respiratory Society. *Eur Respir J* 1993;16(suppl):5-40.
- Standardized lung function testing. Official statement of the European Respiratory Society. *Eur Respir J* 1993;16(suppl):1-100.
- van der Ploeg RJ, Oosterhuis HJ. The "make/break test" as a diagnostic tool in functional weakness. *J Neurol Neurosurg Psychiatry* 1991;54:248-51.
- Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Arch Phys Med Rehabil* 1997;78:26-32.
- Wasserman K, Hansen JE, Sue DY, Whipp BJ. Principles of exercise testing and interpretation. Philadelphia: Lea & Febiger; 2001.
- Carter R, Peavler M, Zinkgraf S, Williams J, Fields S. Predicting maximal exercise ventilation in patients with chronic obstructive pulmonary disease. *Chest* 1987;92:253-9.
- Beaver WL, Wasserman K, Whipp BJ. Improved detection of lactate threshold during exercise using a log-log transformation. *J Appl Physiol* 1985;59:1936-40.
- Folgering H, van Herwaarden C. Exercise limitations in patients with pulmonary diseases. *Int J Sports Med* 1994;15:107-11.
- Miyoshi S, Trulock EP, Schaefer HJ, Hsieh CM, Patterson GA, Cooper JD. Cardiopulmonary exercise testing after single and double lung transplantation. *Chest* 1990;97:1130-6.
- Orens JB, Becker FS, Lynch JP, Christensen PJ, Deeb GM, Martinez FJ. Cardiopulmonary exercise testing following allogeneic lung transplantation for different underlying disease states. *Chest* 1995;107:144-9.
- Gibbons WJ, Levine SM, Bryan CL, et al. Cardiopulmonary exercise responses after single lung transplantation for severe obstructive lung disease. *Chest* 1991;100:106-11.
- Mercier JG, Hokanson JF, Brooks GA. Effects of cyclosporine A on skeletal muscle mitochondrial respiration and endurance time in rats. *Am J Respir Crit Care Med* 1995;151:1532-6.
- Hokanson JF, Mercier JG, Brooks GA. Cyclosporine A decreases rat skeletal muscle mitochondrial respiration in vitro. *Am J Respir Crit Care Med* 1995;151:1848-51.
- Krieger AC, Szidon P, Kesten S. Skeletal muscle dysfunction in lung transplantation. *J Heart Lung Transplant* 2000;19:392-400.
- Ambrosino N, Bruschi C, Callegari G, et al. Time course of exercise capacity, skeletal and respiratory muscle performance after heart-lung transplantation. *Eur Respir J* 1996;9:1508-14.
- Stiebellehner L, Quittan M, End A, et al. Aerobic endurance training program improves exercise performance in lung transplant recipients. *Chest* 1998;113:906-12.
- Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. *Chest* 1991;100:618-23.
- Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:1541-51.
- Serres I, Varray A, Vallet G, Micallef JP, Prefaut C. Improved skeletal muscle performance after individualized exercise training in patients with chronic obstructive pulmonary disease. *J Cardiopulmon Rehabil* 1997;17:232-8.
- Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: the basic questions. *Eur Respir J* 1997;10:2884-91.